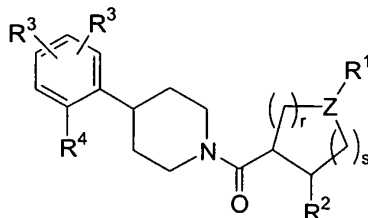


IN THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (original) A compound of structural formula I:



(I)

or a pharmaceutically acceptable salt thereof; wherein:

R¹ is selected from the group consisting of:

- (1) hydrogen,
- (2) amidino,
- (3) C₁₋₄ alkyliminoyl,
- (4) C₁₋₁₀ alkyl,
- (5) -(CH₂)_n-NR⁷R⁸,
- (6) -(CH₂)_n-C₃₋₇ cycloalkyl,
- (7) -(CH₂)_n-phenyl,
- (8) -(CH₂)_n-naphthyl, and
- (9) -(CH₂)_n-heteroaryl,

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R³, and wherein alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R³ and oxo;

R² is selected from the group consisting of:

- (1) phenyl,
- (2) naphthyl, and
- (3) heteroaryl,

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R³;

each R³ is independently selected from the group consisting of:

- (1) hydrogen,
- (2) C₁₋₆ alkyl,
- (3) -(CH₂)_n-phenyl,
- (4) -(CH₂)_n-naphthyl,

- (5) $-(CH_2)_n$ -heteroaryl,
- (6) $-(CH_2)_n$ -heterocycloalkyl,
- (7) $-(CH_2)_n$ C₃₋₇ cycloalkyl,
- (8) halogen,
- (9) OR⁶,
- (10) $-(CH_2)_n$ N(R⁶)₂,
- (11) $-(CH_2)_n$ C≡N,
- (12) $-(CH_2)_n$ CO₂R⁶,
- (13) NO₂,
- (14) $-(CH_2)_n$ NR⁶SO₂R⁶,
- (15) $-(CH_2)_n$ SO₂N(R⁶)₂,
- (16) $-(CH_2)_n$ S(O)_pR⁶,
- (17) $-(CH_2)_n$ NR⁶C(O)N(R⁶)₂,
- (18) $-(CH_2)_n$ C(O)N(R⁶)₂,
- (19) $-(CH_2)_n$ NR⁶C(O)R⁶,
- (20) $-(CH_2)_n$ NR⁶CO₂R⁶,
- (21) $-(CH_2)_n$ NR⁶C(O)-heteroaryl,
- (22) $-(CH_2)_n$ C(O)NR⁶N(R⁶)₂,
- (23) $-(CH_2)_n$ C(O)NR⁶NR⁶C(O)R⁶,
- (24) O(CH₂)_nC(O)N(R⁶)₂,
- (25) CF₃,
- (26) CH₂CF₃,
- (27) OCF₃, and
- (28) OCH₂CF₃,

wherein phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocycloalkyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C₁₋₄ alkyl, trifluoromethyl, and C₁₋₄ alkoxy, and wherein any methylene (CH₂) carbon atom in R³ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl, or wherein two substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

R⁴ is selected from the group consisting of:

- (1) $-(CH_2)_n$ -N(R⁵)-NR⁵R⁶,
- (2) $-(CH_2)_n$ -N(R⁵)-(CH₂)_q-NR⁵R⁶,
- (3) $-(CH_2)_n$ -N(R⁵)-C(=NR⁵)-NR⁵R⁶,
- (4) $-(CH_2)_n$ -N(R⁵)-(CH₂)_q-N(R⁵)-(C=NR⁵)-NR⁵R⁶,
- (5) $-(CH_2)_n$ -N(R⁵)-(CH₂)_n-C(R⁵)(N(R⁵)₂)-(CH₂)_q-OR⁶,
- (6) $-(CH_2)_n$ -N(R⁵)-(CH₂)_n-C(R⁵)(N(R⁵)₂)(CH₂)_n-R⁶,

- (7) $-(CH_2)_n-N(R^5)-(CH_2)_n-C(R^5)(N(R^5)_2)(CH_2)_q-S(O)_p-R^6$,
- (8) $-(CH_2)_n-N(R^5)-(CH_2)_n-C(R^5)(N(R^5)_2)(CH_2)_q-NR^5R^6$,
- (9) $-(CH_2)_n-N(R^5)-C(O)(CH_2)_n-C(R^5)(N(R^5)_2)(CH_2)_n-R^6$,
- (10) $-(CH_2)_n-N(R^5)-C(O)(CH_2)_n-C(R^5)(N(R^5)_2)(CH_2)_q-S(O)_p-R^6$,
- (11) $-(CH_2)_n-N(R^5)-C(O)(CH_2)_n-C(R^5)(N(R^5)_2)(CH_2)_q-NR^5R^6$,
- (12) $-(CH_2)_n-N(R^5)-C(O)(CH_2)_n-C(R^5)(N(R^5)_2)(CH_2)_q-O-R^6$, and
- (13) $-(CH_2)_n-N(R^5)-R^9$,

wherein $(CH_2)_n$ is unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, oxo, and C₁₋₄ alkoxy;

R⁵ is selected from the group consisting of:

- (1) hydrogen,
- (2) C₁₋₆ alkyl, and
- (3) C(O)C₁₋₆ alkyl,

wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, oxo, and C₁₋₄ alkoxy;

R⁶ is selected from the group consisting of:

- (1) hydrogen,
- (2) C₁₋₆ alkyl,
- (3) C(O)C₁₋₆ alkyl,
- (4) $-(CH_2)_nC_{3-7}$ cycloalkyl,
- (5) $-(CH_2)_nC_{2-7}$ heterocycloalkyl,
- (6) $-(CH_2)_n$ -phenyl,
- (7) $-(CH_2)_n$ -naphthyl,
- (8) $-(CH_2)_n$ -heteroaryl, and
- (9) $-(CH_2)_nC_{3-7}$ bicycloalkyl,

wherein alkyl, phenyl, heteroaryl, heterocycloalkyl, naphthyl, cycloalkyl, bicycloalkyl and $(CH_2)_n$ are unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, and C₁₋₄ alkoxy, or wherein two R⁶ groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and -NC₁₋₄ alkyl;

each R⁷ and R⁸ is independently selected from the group consisting of:

- (1) hydrogen,
- (2) amidino,
- (3) C₁₋₄ alkyliminoyl,
- (4) C₁₋₁₀ alkyl,
- (5) $-(CH_2)_nC_{3-7}$ cycloalkyl,
- (6) $-(CH_2)_n$ -phenyl,

(7) $-(\text{CH}_2)_n$ -naphthyl, and

(8) $-(\text{CH}_2)_n$ -heteroaryl,

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^3 , and wherein alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^3 and oxo;

R^9 is selected from the group consisting of:

- (1) alanine,
- (2) glycine,
- (3) proline,
- (4) cysteine,
- (5) histidine,
- (6) glutamine,
- (7) aspartic acid,
- (8) isoleucine,
- (9) arginine,
- (10) glutamic acid,
- (11) lysine,
- (12) serine,
- (13) phenylalanine,
- (14) leucine,
- (15) threonine,
- (16) tryptophan,
- (17) methionine,
- (18) valine,
- (19) tyrosine,
- (20) asparagine,
- (21) 2-aminoadipic acid,
- (22) beta-alanine,
- (23) 2-aminoheptanedioic acid,
- (24) 2-aminobutyric acid,
- (25) 4-aminobutyric acid,
- (26) 2,4-diaminobutyric acid,
- (27) citrulline,
- (28) cycloserine,
- (29) norvaline,
- (30) norleucine,
- (31) ornithine,

- (32) penicillamine,
- (33) phenylglycine,
- (34) phenylisoserine,
- (35) phenylstatine,
- (36) pipercolic acid,
- (37) piperidine carboxylic acid,
- (38) pyroglutamic acid,
- (39) sarcosine,
- (40) statine,
- (41) allo-threonine,
- (42) t-leucine,
- (43) 2-aminoisobutyric acid, and
- (44) 3-aminoisobutyric acid;

Z is selected from the group consisting of:

- (1) C(R¹), and
- (2) N;

r is 1 or 2;

s is 0, 1, or 2;

n is 0, 1, 2, or 3;

p is 0, 1, or 2; and

q is 1, 2, 3, or 4.

2. (original) The compound of Claim 1 wherein R¹ is selected from the group consisting of: hydrogen, C₁₋₆ alkyl, -(CH₂)₀₋₁C₃₋₆ cycloalkyl, and -(CH₂)₀₋₁-phenyl, wherein phenyl is unsubstituted or substituted with one to three groups independently selected from R³, and alkyl and cycloalkyl are optionally substituted with one to three groups independently selected from R³ and oxo; and pharmaceutically acceptable salts thereof.

3. (original) The compound of Claim 2 wherein R² is phenyl or thienyl, optionally substituted with one to three groups independently selected from R³; and pharmaceutically acceptable salts thereof.

4. (original) The compound of Claim 3 wherein R² is phenyl optionally substituted with one to three groups independently selected from R³; and pharmaceutically acceptable salts thereof.

5. (original) The compound of Claim 1 wherein each R³ is independently selected from the group consisting of: C₁₋₆ alkyl, -(CH₂)_n-phenyl, -(CH₂)_n-heteroaryl,

$-(CH_2)_n C_{2-7}$ heterocycloalkyl, $-(CH_2)_n C_{3-7}$ cycloalkyl, halogen, OR^5 , $-(CH_2)_n N(R^5)_2$, $-(CH_2)_n CO_2 R^5$, NO_2 , and CF_3 , wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy, and wherein alkyl, cycloalkyl, heterocycloalkyl, and $(CH_2)_n$ are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy, or wherein two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group; and pharmaceutically acceptable salts thereof.

6. (original) The compound of Claim 1 wherein R^4 is selected from the group consisting of:

- (1) $-(CH_2)_n N(R^5)-NH_2$,
- (2) $-(CH_2)_n N(R^5)-(CH_2)_q NH_2$,
- (3) $-(CH_2)_n N(R^5)-(CH_2)_n NR^5 R^6$,
- (4) $-(CH_2)_n N(R^5)-(CH_2)_n NHC_{1-6} \text{ alkyl}$,
- (5) $-(CH_2)_n N(R^5)-(CH_2)_n N(C_{1-6} \text{ alkyl})_2$,
- (6) $-(CH_2)_n N(R^5)-(CH_2)_n NHC(O)C_{1-6} \text{ alkyl}$,
- (7) $-(CH_2)_n N(R^5)-(CH_2)_n N(R^5)C(O)C_{1-6} \text{ alkyl}$,
- (8) $-(CH_2)_n N(R^5)-(CH_2)_n N(C(O)C_{1-6} \text{ alkyl})_2$,
- (9) $-(CH_2)_n N(R^5)-C(=NH)-NH_2$,
- (10) $-(CH_2)_n N(R^5)-(CH_2)_q NH(C=NH)-NH_2$, $2n^5 2n^2$
- (11) $-(CH_2)_n N(R^5)-(CH_2)_n C(R^5)(NH_2)(CH_2)_q OH$,
- (12) $-(CH_2)_n N(R^5)-(CH_2)_n C(R^5)(NH_2)(CH_2)_q OC_{1-6} \text{ alkyl}$,
- (13) $-(CH_2)_n N(R^5)-(CH_2)_n C(R^5)(NH_2)(CH_2)_q OR^6$,
- (14) $-(CH_2)_n N(R^5)-(CH_2)_n C(R^5)(NH_2)(CH_2)_n \text{-heteroaryl}$,
- (15) $-(CH_2)_n N(R^5)-(CH_2)_n C(R^5)(NH_2)(CH_2)_n R^6$,
- (16) $-(CH_2)_n N(R^5)-(CH_2)_n C(R^5)(NH_2)(CH_2)_q SH$,
- (17) $-(CH_2)_n N(R^5)-(CH_2)_n C(R^5)(NH_2)(CH_2)_q S-C_{1-6} \text{ alkyl}$,
- (18) $-(CH_2)_n N(R^5)-(CH_2)_n C(R^5)(NH_2)(CH_2)_q S-R^6$,
- (19) $-(CH_2)_n N(R^5)-(CH_2)_n C(R^5)(NH_2)(CH_2)_q NH_2$,
- (20) $-(CH_2)_n N(R^5)-(CH_2)_n C(R^5)(NH_2)(CH_2)_q NHR^6$,
- (21) $-(CH_2)_n N(R^5)-(CH_2)_n C(R^5)(NH_2)(CH_2)_q NR^5 R^6$,
- (22) $-(CH_2)_n N(R^5)-C(O)(CH_2)_n C(R^5)(NH_2)(CH_2)_n \text{-heteroaryl}$,
- (23) $-(CH_2)_n N(R^5)-C(O)(CH_2)_n C(R^5)(NH_2)(CH_2)_q SH$,
- (24) $-(CH_2)_n N(R^5)-C(O)(CH_2)_n C(R^5)(NH_2)(CH_2)_q S-C_{1-6} \text{ alkyl}$,
- (25) $-(CH_2)_n N(R^5)-C(O)(CH_2)_n C(R^5)(NH_2)(CH_2)_q NR^5 R^6$, and
- (26) $-(CH_2)_n N(R^5)-R^9$,

wherein alkyl and $(CH_2)_n$ are unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, oxo, and C₁₋₄ alkoxy, and heteroaryl is unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, and C₁₋₄ alkoxy; and pharmaceutically acceptable salts thereof.

7. (original) The compound of Claim 1 wherein R⁶ is selected from the group consisting of: hydrogen, C₁₋₆ alkyl, C(O)C₁₋₆ alkyl, and $-(CH_2)_n$ -heteroaryl; and pharmaceutically acceptable salts thereof.

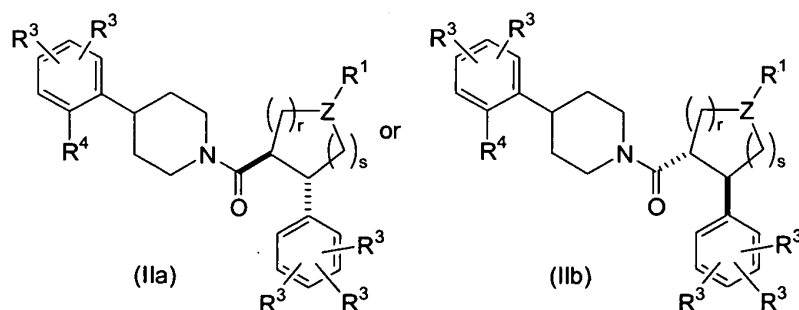
8. (original) The compound of Claim 5 wherein Z is CR¹; and pharmaceutically acceptable salts thereof.

9. (original) The compound of Claim 6 wherein Z is N; and pharmaceutically acceptable salts thereof.

10. (original) The compound of Claim 1 wherein r is 1 and s is 1; and pharmaceutically acceptable salts thereof.

11. (original) The compound of Claim 1 wherein r is 2 and s is 1; and pharmaceutically acceptable salts thereof.

12. (original) The compound of Claim 1 of structural formula IIa or IIb of the indicated *trans* relative stereochemical configuration:



or a pharmaceutically acceptable salt thereof; wherein:

R¹ is selected from the group consisting of: hydrogen, amidino, C₁₋₄ alkylimino, C₁₋₆ alkyl, C₅₋₆ cycloalkyl, $-(CH_2)_{0-1}$ phenyl, and $-(CH_2)_{0-1}$ heteroaryl, wherein phenyl and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R³, and wherein

alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^3 and oxo;

each R^3 is independently selected from the group consisting of:

- (1) hydrogen,
- (2) C_{1-6} alkyl,
- (3) $-(CH_2)_n$ -phenyl,
- (4) $-(CH_2)_n$ -naphthyl,
- (5) $-(CH_2)_n$ -heteroaryl,
- (6) $-(CH_2)_n$ -heterocycloalkyl,
- (7) $-(CH_2)_n C_{3-7}$ cycloalkyl,
- (8) halogen,
- (9) OR^{64} ,
- (10) $-(CH_2)_n N(R^{64})_2$,
- (11) $-(CH_2)_n C \equiv N$,
- (12) $-(CH_2)_n CO_2 R^{64}$,
- (13) NO_2 ,
- (14) $-(CH_2)_n NR^4 SO_2 R^{64}$,
- (15) $-(CH_2)_n SO_2 N(R^{64})_2$,
- (16) $-(CH_2)_n S(O)_{0-1} R^{64}$,
- (17) $-(CH_2)_n NR^{64} C(O) N(R^{64})_2$,
- (18) $-(CH_2)_n C(O) N(R^{64})_2$,
- (19) $-(CH_2)_n NR^{64} C(O) R^{64}$,
- (20) $-(CH_2)_n NR^{64} CO_2 R^{64}$,
- (21) $-(CH_2)_n NR^{64} C(O)$ -heteroaryl,
- (22) $-(CH_2)_n C(O) NR^{64} N(R^{64})_2$,
- (23) $-(CH_2)_n C(O) NR^{64} NR^{64} C(O) R^{64}$,
- (24) $O(CH_2)_n C(O) N(R^{64})_2$,
- (25) CF_3 ,
- (26) $CH_2 CF_3$,
- (27) OCF_3 , and
- (28) $OCH_2 CF_3$,

wherein phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocycloalkyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy, and wherein any methylene (CH_2) carbon atom in R^3 is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy,

and C₁₋₄ alkyl, or wherein two substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

R⁴ is selected from the group consisting of:

- (1) -(CH₂)-N(R⁵)-NR⁵R⁶,
- (2) -(CH₂)-N(R⁵)-(CH₂)₁₋₃-NR⁵R⁶,
- (3) -(CH₂)-N(R⁵)-C(=NR⁵)-NR⁵R⁶,
- (4) -(CH₂)-N(R⁵)-(CH₂)₁₋₃-N(R⁵)-(C=NR⁵)-NR⁵R⁶,
- (5) -(CH₂)-N(R⁵)-(CH₂)₀₋₂-C(R⁵)(N(R⁵)₂)-(CH₂)₁₋₂-OR⁶,
- (6) -(CH₂)-N(R⁵)-(CH₂)₀₋₂-C(R⁵)(N(R⁵)₂)(CH₂)₁₋₂-R⁶,
- (7) -(CH₂)-N(R⁵)-(CH₂)₀₋₂-C(R⁵)(N(R⁵)₂)(CH₂)₁₋₂-S-R⁶,
- (8) -(CH₂)-N(R⁵)-(CH₂)₀₋₂-C(R⁵)(N(R⁵)₂)(CH₂)₁₋₄-NR⁵R⁶,
- (9) -(CH₂)-N(R⁵)-C(O)(CH₂)₀₋₂-C(R⁵)(N(R⁵)₂)(CH₂)₁₋₂-R⁶,
- (10) -(CH₂)-N(R⁵)-C(O)(CH₂)₀₋₂-C(R⁵)(N(R⁵)₂)(CH₂)₁₋₂-S-R⁶,
- (11) -(CH₂)-N(R⁵)-C(O)(CH₂)₀₋₂-C(R⁵)(N(R⁵)₂)(CH₂)₁₋₄-NR⁵R⁶, and
- (12) -(CH₂)-N(R⁵)-R⁹,

wherein (CH₂)_n is unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, oxo, and C₁₋₄ alkoxy;

R⁵ is selected from the group consisting of:

- (1) hydrogen,
- (2) C₁₋₆ alkyl, and
- (3) C(O)C₁₋₆ alkyl,

wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, oxo, and C₁₋₄ alkoxy;

R⁶ is selected from the group consisting of:

- (1) hydrogen,
- (2) C₁₋₆ alkyl,
- (3) C(O)C₁₋₆ alkyl,
- (4) -(CH₂)_nC₃₋₇ cycloalkyl,
- (5) -(CH₂)_nC₂₋₇ heterocycloalkyl,
- (6) -(CH₂)_n-phenyl,
- (7) -(CH₂)_n-naphthyl,
- (8) -(CH₂)_n-heteroaryl, and
- (9) -(CH₂)_nC₃₋₇ bicycloalkyl,

wherein alkyl, phenyl, heteroaryl, heterocycloalkyl, naphthyl, cycloalkyl, bicycloalkyl and (CH₂)_n are unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, and C₁₋₄ alkoxy, or wherein two R⁶ groups together with the atom to which they are

attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and -NC₁₋₄ alkyl;

each R⁷ and R⁸ is independently selected from the group consisting of:

- (1) hydrogen,
- (2) amidino,
- (3) C₁₋₄ alkyliminoyl,
- (4) C₁₋₁₀ alkyl,
- (5) -(CH₂)_n-C₃₋₇ cycloalkyl,
- (6) -(CH₂)_n-phenyl,
- (7) -(CH₂)_n-naphthyl, and
- (8) -(CH₂)_n-heteroaryl,

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R³, and wherein alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R³ and oxo;

R⁹ is selected from the group consisting of:

- (1) alanine,
- (2) glycine,
- (3) proline,
- (4) cysteine,
- (5) histidine,
- (6) glutamine,
- (7) aspartic acid,
- (8) isoleucine,
- (9) arginine,
- (10) glutamic acid,
- (11) lysine,
- (12) serine,
- (13) phenylalanine,
- (14) leucine,
- (15) threonine,
- (16) tryptophan,
- (17) methionine,
- (18) valine,
- (19) tyrosine,
- (20) asparagine,
- (21) 2-aminoadipic acid,
- (22) beta-alanine,

- (23) 2-aminoheptanedioic acid,
- (24) 2-aminobutyric acid,
- (25) 4-aminobutyric acid,
- (26) 2,4-diaminobutyric acid,
- (27) citrulline,
- (28) cycloserine,
- (29) norvaline,
- (30) norleucine,
- (31) ornithine,
- (32) penicillamine,
- (33) phenylglycine,
- (34) phenylisoserine,
- (35) phenylstatine,
- (36) pipecolic acid,
- (37) piperidine carboxylic acid,
- (38) pyroglutamic acid,
- (39) sarcosine,
- (40) statine,
- (41) allo-threonine,
- (42) t-leucine,
- (43) 2-aminoisobutyric acid, and
- (44) 3-aminoisobutyric acid;

Z is selected from the group consisting of:

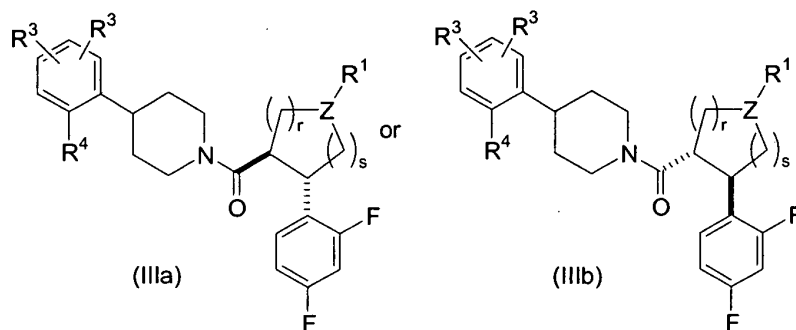
- (1) C(R¹), and
- (2) N;

r is 1 or 2;

s is 0, 1, or 2; and

n is 0, 1, 2, 3 or 4.

13. (original) The compound of Claim 1 of structural formula IIIa or IIIb of the indicated *trans* relative stereochemical configuration:



or a pharmaceutically acceptable salt thereof; wherein:

R¹ is selected from the group consisting of: hydrogen, C₁₋₄ alkyl, and -(CH₂)₀₋₁ phenyl;

each R³ is independently selected from the group consisting of:

- (1) hydrogen,
- (2) C₁₋₆ alkyl,
- (3) -(CH₂)_n-phenyl,
- (4) -(CH₂)_n-naphthyl,
- (5) -(CH₂)_n-heteroaryl,
- (6) -(CH₂)_n-heterocycloalkyl,
- (7) -(CH₂)_nC₃₋₇ cycloalkyl,
- (8) halogen,
- (9) OR⁶⁴,
- (10) -(CH₂)_nN(R⁶⁴)₂,
- (11) -(CH₂)_nC≡N,
- (12) -(CH₂)_nCO₂R⁶⁴,
- (13) NO₂,
- (14) -(CH₂)_nNR⁶⁴SO₂R⁶⁴,
- (15) -(CH₂)_nSO₂N(R⁶⁴)₂,
- (16) -(CH₂)_nS(O)₀₋₁R⁶⁴,
- (17) -(CH₂)_nNR⁶⁴C(O)N(R⁶⁴)₂,
- (18) -(CH₂)_nC(O)N(R⁶⁴)₂,
- (19) -(CH₂)_nNR⁶⁴C(O)R⁶⁴,
- (20) -(CH₂)_nNR⁶⁴CO₂R⁶⁴,
- (21) -(CH₂)_nNR⁶⁴C(O)-heteroaryl,
- (22) -(CH₂)_nC(O)NR⁶⁴N(R⁶⁴)₂,
- (23) -(CH₂)_nC(O)NR⁶⁴NR⁶⁴C(O)R⁶⁴,
- (24) O(CH₂)_nC(O)N(R⁶⁴)₂,
- (25) CF₃,

- (26) CH_2CF_3 ,
- (27) OCF_3 , and
- (28) OCH_2CF_3 ,

wherein phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocycloalkyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy, and wherein any methylene (CH_2) carbon atom in R^3 is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl, or wherein two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

R^4 is selected from the group consisting of:

- (1) $-(\text{CH}_2)-\text{N}(\text{R}^5)-\text{NR}^5\text{R}^6$,
- (2) $-(\text{CH}_2)-\text{N}(\text{R}^5)-(\text{CH}_2)_{1-3}-\text{NR}^5\text{R}^6$,
- (3) $-(\text{CH}_2)-\text{N}(\text{R}^5)-\text{C}(=\text{NR}^5)-\text{NR}^5\text{R}^6$,
- (4) $-(\text{CH}_2)-\text{N}(\text{R}^5)-(\text{CH}_2)_{1-3}-\text{N}(\text{R}^5)-(\text{C}=\text{NR}^5)-\text{NR}^5\text{R}^6$,
- (5) $-(\text{CH}_2)-\text{N}(\text{R}^5)-(\text{CH}_2)_{0-2}-\text{C}(\text{R}^5)(\text{N}(\text{R}^5)_2)-(\text{CH}_2)_{1-2}-\text{OR}^6$,
- (6) $-(\text{CH}_2)-\text{N}(\text{R}^5)-(\text{CH}_2)_{0-2}-\text{C}(\text{R}^5)(\text{N}(\text{R}^5)_2)(\text{CH}_2)_{1-2}-\text{R}^6$,
- (7) $-(\text{CH}_2)-\text{N}(\text{R}^5)-(\text{CH}_2)_{0-2}-\text{C}(\text{R}^5)(\text{N}(\text{R}^5)_2)(\text{CH}_2)_{1-2}-\text{S}-\text{R}^6$,
- (8) $-(\text{CH}_2)-\text{N}(\text{R}^5)-(\text{CH}_2)_{0-2}-\text{C}(\text{R}^5)(\text{N}(\text{R}^5)_2)(\text{CH}_2)_{1-4}-\text{NR}^5\text{R}^6$,
- (9) $-(\text{CH}_2)-\text{N}(\text{R}^5)-\text{C}(\text{O})(\text{CH}_2)_{0-2}-\text{C}(\text{R}^5)(\text{N}(\text{R}^5)_2)(\text{CH}_2)_{1-2}-\text{R}^6$,
- (10) $-(\text{CH}_2)-\text{N}(\text{R}^5)-\text{C}(\text{O})(\text{CH}_2)_{0-2}-\text{C}(\text{R}^5)(\text{N}(\text{R}^5)_2)(\text{CH}_2)_{1-2}-\text{S}-\text{R}^6$,
- (11) $-(\text{CH}_2)-\text{N}(\text{R}^5)-\text{C}(\text{O})(\text{CH}_2)_{0-2}-\text{C}(\text{R}^5)(\text{N}(\text{R}^5)_2)(\text{CH}_2)_{1-4}-\text{NR}^5\text{R}^6$, and
- (12) $-(\text{CH}_2)-\text{N}(\text{R}^5)-\text{R}^9$,

wherein $(\text{CH}_2)_n$ is unsubstituted or substituted with one to three groups independently selected from halogen, C_{1-4} alkyl, hydroxy, oxo, and C_{1-4} alkoxy;

R^5 is selected from the group consisting of:

- (1) hydrogen,
- (2) C_{1-6} alkyl, and
- (3) $\text{C}(\text{O})\text{C}_{1-6}$ alkyl,

wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, C_{1-4} alkyl, hydroxy, oxo, and C_{1-4} alkoxy;

R^6 is selected from the group consisting of:

- (1) hydrogen,
- (2) C_{1-6} alkyl,
- (3) $\text{C}(\text{O})\text{C}_{1-6}$ alkyl,
- (4) $-(\text{CH}_2)_n\text{C}_{3-7}$ cycloalkyl,
- (5) $-(\text{CH}_2)_n\text{C}_{2-7}$ heterocycloalkyl,
- (6) $-(\text{CH}_2)_n$ -phenyl,

- (7) $-(CH_2)_n$ -naphthyl,
- (8) $-(CH_2)_n$ -heteroaryl, and
- (9) $-(CH_2)_n$ C₃₋₇ bicycloalkyl,

wherein alkyl, phenyl, heteroaryl, heterocycloalkyl, naphthyl, cycloalkyl, bicycloalkyl and $(CH_2)_n$ are unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, and C₁₋₄ alkoxy, or wherein two R⁶ groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and -NC₁₋₄ alkyl;

each R⁷ and R⁸ is independently selected from the group consisting of:

- (1) hydrogen,
- (2) amidino,
- (3) C₁₋₄ alkyliminoyl,
- (4) C₁₋₁₀ alkyl,
- (5) $-(CH_2)_n$ -C₃₋₇ cycloalkyl,
- (6) $-(CH_2)_n$ -phenyl,
- (7) $-(CH_2)_n$ -naphthyl, and
- (8) $-(CH_2)_n$ -heteroaryl,

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R³, and wherein alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R³ and oxo;

R⁹ is selected from the group consisting of:

- (1) alanine,
- (2) glycine,
- (3) proline,
- (4) cysteine,
- (5) histidine,
- (6) glutamine,
- (7) aspartic acid,
- (8) isoleucine,
- (9) arginine,
- (10) glutamic acid,
- (11) lysine,
- (12) serine,
- (13) phenylalanine,
- (14) leucine,
- (15) threonine,
- (16) tryptophan,

- (17) methionine,
- (18) valine,
- (19) tyrosine,
- (20) asparagine,
- (21) 2-aminoadipic acid,
- (22) beta-alanine,
- (23) 2-aminoheptanedioic acid,
- (24) 2-aminobutyric acid,
- (25) 4-aminobutyric acid,
- (26) 2,4-diaminobutyric acid,
- (27) citrulline,
- (28) cycloserine,
- (29) norvaline,
- (30) norleucine,
- (31) ornithine,
- (32) penicillamine,
- (33) phenylglycine,
- (34) phenylisoserine,
- (35) phenylstatine,
- (36) pipecolic acid,
- (37) piperidine carboxylic acid,
- (38) pyroglutamic acid,
- (39) sarcosine,
- (40) statine,
- (41) allo-threonine,
- (42) t-leucine,
- (43) 2-aminoisobutyric acid, and
- (44) 3-aminoisobutyric acid;

Z is selected from the group consisting of:

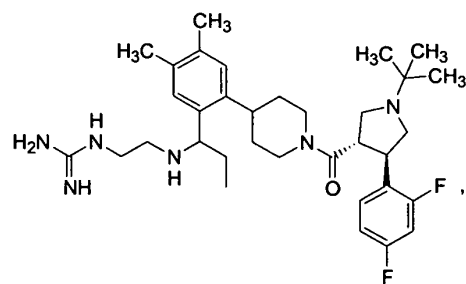
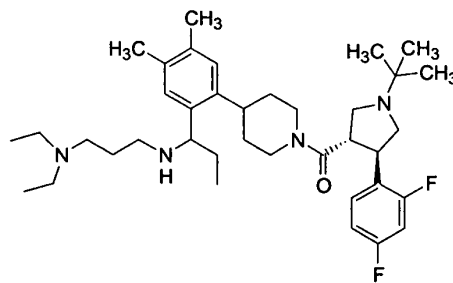
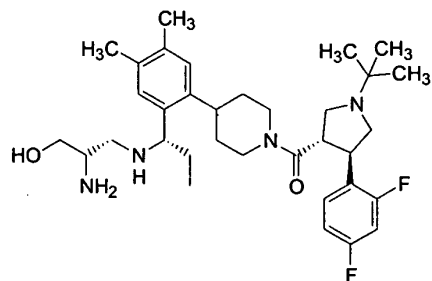
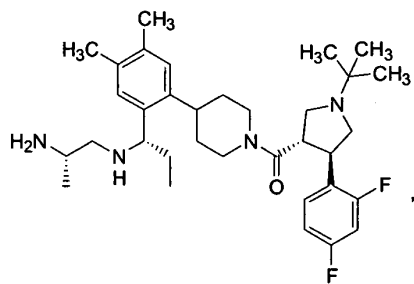
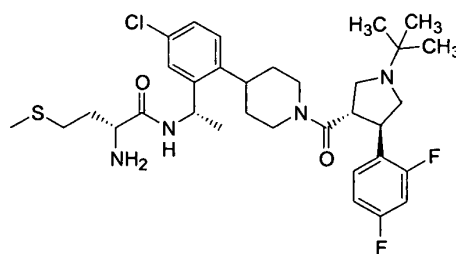
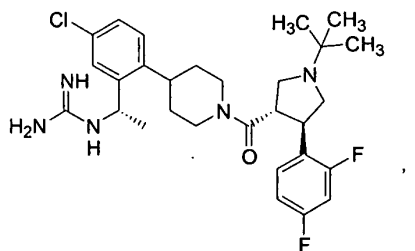
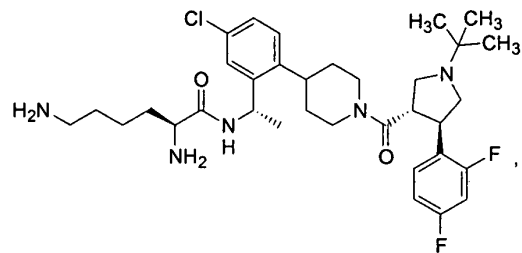
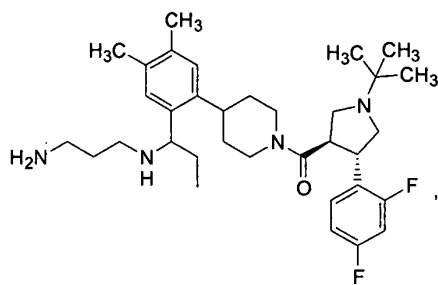
- (1) C(R¹), and
- (2) N;

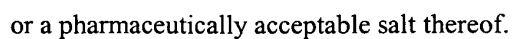
r is 1 or 2;

s is 0, 1, or 2; and

n is 0, 1, 2, 3, or 4.

14. (original) The compound of Claim 13 selected from the group consisting of:



CC1=C(C)C(C2=CC=C(C=C2)NCCN)=C(C3CCN(C3)C(=O)C4CC(C)(C)N4C5=CC=C(F)C=C5)C1

or a pharmaceutically acceptable salt thereof.

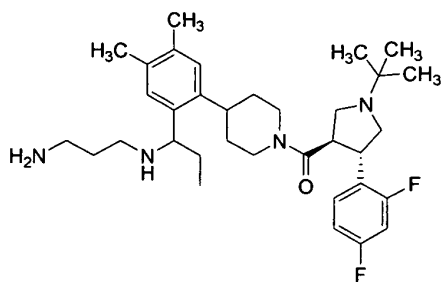
CC(C)(C)N1CC[C@H](C1C(=O)N2CC[C@@H](C2)c3cc(F)cc(F)c3)C(=O)N4CC[C@@H](C4)C(=O)N[C@@H](Cc5ccc(Cl)cc5)C(=O)N[C@@H](CCCCN)C(=O)N

or a pharmaceutically acceptable salt thereof.

CC(C)(C)N1CC[C@H](C2=CC=C(F)C=C2)C1C(=O)N3CCCC[C@H]3C4=CC=C(Cl)C=C4NC(=N)N

or a pharmaceutically acceptable salt thereof.

18. (original) The compound of Claim 14 which is:



or a pharmaceutically acceptable salt thereof.

19. (original) A method for the treatment or prevention of disorders, diseases or conditions responsive to the activation of the melanocortin-4 receptor in a mammal in need thereof which comprises administering to the mammal a therapeutically or prophylactically effective amount of a compound according to Claim 1.

20. (currently amended) A method for the treatment or prevention of obesity, diabetes mellitus, male sexual dysfunction, female sexual dysfunction or erectile dysfunction in a mammal in need thereof which comprises administering to the mammal a therapeutically or prophylactically effective amount of a compound according to Claim 1.

Claims 21 - 23 (canceled)

24. (original) A pharmaceutical composition which comprises a compound of Claim 1 and a pharmaceutically acceptable carrier.

Claims 25 - 27 (canceled)

28. (currently amended) A method of treating or preventing erectile dysfunction in a mammal in need thereof comprising administering to the mammal a therapeutically effective or prophylactically effective amount of a compound of Claim 1 in combination with a type V cyclic-GMP-selective phosphodiesterase inhibitor, an α 2-adrenergic receptor antagonist, or a dopaminergic agent.

Claims 29 - 30 (canceled)

31. (currently amended) A method of treating or preventing diabetes or obesity in a mammal in need thereof comprising administering to the mammal a therapeutically effective or prophylactically effective amount of a compound of Claim 1 in combination with an insulin sensitizer, an insulin mimetic, a sulfonylurea, an α -glucosidase inhibitor, a HMG-CoA reductase inhibitor, a serotonergic agent, a β 3-adrenoreceptor agonist, a neuropeptide Y1 antagonist, a neuropeptide Y5 antagonist, a pancreatic lipase inhibitor, a cannabinoid CB₁ receptor antagonist or inverse agonist, a melanin-concentrating hormone receptor antagonist, a bombesin receptor subtype 3 agonist, a ghrelin receptor antagonist, or a dipeptidyl peptidase IV inhibitor.

32. (currently amended) A method of treating or preventing an obesity-related disorder selected from the group consisting of: overeating, binge eating, and bulimia, hypertension, diabetes, elevated plasma insulin concentrations, insulin resistance, dyslipidemias, hyperlipidemia, endometrial, breast, prostate and colon cancer, osteoarthritis, obstructive sleep apnea, cholelithiasis, gallstones, heart disease, abnormal heart rhythms and arrhythmias, myocardial infarction, congestive heart failure, coronary heart disease, sudden death, stroke, polycystic ovary disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, GH-deficient subjects, normal variant short stature, Turner's syndrome, metabolic syndrome, insulin resistance syndrome, sexual and reproductive dysfunction, infertility, hypogonadism, hirsutism, obesity-related gastro-esophageal reflux, Pickwickian syndrome, cardiovascular disorders, inflammation, systemic inflammation of the vasculature, arteriosclerosis, hypercholesterolemia, hyperuricaemia, lower back pain, gallbladder disease, gout, and kidney cancer, cardiac hypertrophy and left ventricular hypertrophy, in a mammal in need thereof which comprises administering to the mammal a therapeutically or prophylactically effective amount of a compound according to Claim 1.

Claims 33 - 42 (canceled)